

## **REMARKS**

### **Rejection of Claims 8-10 Under 35 U.S.C. §101**

Claims 8-10 were rejected under 35 U.S.C. § 101 on grounds that "use" is not a proper statutory class. Claim 8 is amended above to be in the form of a method of treatment claim. Claims 9 and 10 are cancelled. Withdrawal of the rejection of claims 8-10 under 35 U.S.C. § 101 is respectfully requested.

### **Rejection of Claims 7 and 10 Under 35 U.S.C. §101 and §112, First Paragraph**

Claims 7 and 10 are rejected under 35 U.S.C. § 101. Claim 7 is amended above to replace "control" by the term "treatment" as suggested by the examiner.

Claims 7 and 10 are also rejected under § 112, first paragraph. This rejection is discussed below.

### **Rejection of Claims 1-20 Under 35 U.S.C. §112, First Paragraph**

Claims 1-20 are rejected under 35 U.S.C. § 112, first paragraph, on grounds that the specification allegedly does not enable one skilled in the art to make or use the invention as claimed. This rejection is respectfully traversed.

In the rejection reference is made to Applicants' disclosure that the compounds of the claimed genus can be used for treating certain diseases. See, for example, page 3, line 29 - page 4, line 6.

Firstly, it is noted that this is not the only activity/utility described in applicants' specification for the claimed subject matter. For example, Applicants' specification discloses that the compounds can be employed as anti-microbial agents. See page 4, lines 7-14. In addition Applicants' specification discloses that the compounds can be used in preparing agents for *in vivo* diagnostics by, for example, being substituted by a radio-active or UV-detectable residue. See page 4, lines 15-21. Applicants' also disclose that the compounds can be used in studying the metabolism of blood platelets and intracellular signal mechanisms of the fibrinogen receptor through incorporation of a detectable unit, i.e., a "label". See page 4, lines 22-30. Moreover, compounds of formula I can be used as integrin ligands for affinity chromatography columns used in the preparation of integrins in pure form.

See page 20, lines 20-36 of Applicants' specification. The enablement requirement is satisfied if the disclosure objectively enables any mode of making and using the claimed invention. See, e.g., *Engel Industires Inc. v. The Lockformer Co.*, 20 USPQ 2d 1300, 1304 (Fed. Cir. 1991) and *Chemcast Corp. v. Arco Indus Corp.*, 16 USPQ 2d 1033, 1037 (Fed. Cir. 1990).

In the rejection it is again argued that the compounds of the claimed genus have not been shown to be useful in any assay. Further, it is argued that it is Applicants' burden to establish that the compounds can be used in accordance with the asserted utility.

However, Applicants respectfully submit that it is the initial burden of the PTO to establish a reason to doubt the veracity of the statements presented in the specification concerning utility. See, e.g., *In re Marzocchi et al.*, 169 USPQ 367, 370 (CCPA 1971) ["...it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure...."] In the instant case, the rationale presented is the asserted lack of a specific example for use of the compounds in an assay. However, this does not establish a reason to doubt the veracity of the statements of utility in Applicants' specification. Applicants' specification provides a specific and useful teaching. It describes a genus of compounds and it describes not one but several utilities for the compounds of the genus.

Moreover, Applicants clearly describe in their specification suitable assays for determining the relative activity of the compounds of the claimed genus. See, for example, the assay concerning integrin inhibitory action at page 2, lines 24-36. See also the discussion of angiogenesis and the interaction between vascular integrins and extracellular matrix proteins, as well as the inhibition of this interaction and the initiation of apoptosis using a cyclic peptide. (See page 2, line 37- page 3, line 8). In addition, at page 4, lines 11-14 Applicants specification cites an article describing an assay for determination of anti-microbial activity.

Using these assays one of ordinary skill in the art with no more than routine experimentation can readily determine the relative activities of any of the compounds of the claimed genus. It is by well settled law that the test for enablement is not whether any experimentation is needed but whether or not that experimentation is undue. See, *In re Angstadt*, 190 USPQ 214, 219 (CCPA 1976). Even a considerable amount of

experimentation is permissible if it is routine. See, e.g., *Ex parte Jackson*, 217 USPQ 804, 807 (POBA 1982). Even if the experimentation needed is complex that does not necessarily make the experimentation undue under the enablement requirement. See also, for example, *In re Wands*, 8 USPQ 2nd 1400, 1404 (Fed. Cir. 1988) ["Enablement is not precluded by the necessity for routine experimentation."].

The asserted utilities in Applicants' specification are not unreasonable to one of ordinary skill in the art. This is exemplified by the fact that the prior art recognizes assays for determining these activities. Moreover, as noted in Applicants' specification, the prior art discloses that other cyclic peptides are described as having similar activity to that described in Applicants' specification. See, e.g., page 2, lines 22-32 of DE 43 10 643 and page 2, lines 19-30 of EP 0 683 173. Thus, one of ordinary skill in the art is presented with no reason to doubt the veracity of Applicants' statements in the specification concerning the activity of the compounds. Merely because it is asserted that a specific example of an assay is not presented in the specification does not lead one of ordinary skill in the art to doubt the veracity of the statements concerning activity. The nature of the invention and the state of the prior art further demonstrate that Applicants' specification provides sufficient guidance to objectively enable one of ordinary skill in the art to make and use the claimed invention.

In view of the above it is respectfully submitted that the rejection fails to present sufficient reason to doubt the veracity that of the statements in Applicants' specification concerning utility. The primary basis for the rejection is an asserted lack of specific example in regards to an assay. However, this does not present a reason to doubt the veracity of the utility statements.

In regards to the terms "physiologically acceptable" and "pharmaceutical" in claims 1, 3 and 6, it is respectfully submitted that these terms do not render the claims non enabled for the reasons discussed above. Moreover, it is respectfully submitted that the terms "physiologically acceptable" and "pharmaceutical" are sufficiently definite to one of ordinary skill in the art. One of ordinary skill in the art can readily determine the scope of the claims. Regardless of the implications stated by the examiner, a physiologically acceptable salt is sufficiently definite to one of ordinary skill in the art regardless of whether the salt is present in a vial or is administered to a patient.

Regarding process claim 4, it is unnecessary for a process claim to recite reaction conditions. See, e.g., *Ex parte Jackson*, 217 USPQ 804, 806 (POBA 1982). Moreover, a process claim is inherently functional. In other words, the literal scope of a process claim only describes those embodiments which actually perform the asserted process. Thus, the literal scope of claim 4 does not include reaction processes that fail to proceed for a sufficient amount of time to obtain the stated result nor does it encompass reaction conditions which are ineffective to obtain the stated result. In addition, it is unnecessary for a process claim to recite the further step of isolating a prepared compound. A compound is prepared by a reaction process regardless of whether it is present in the reaction medium or whether is subjected to a further purification/isolation step.

With regards to the use of brackets in claim 3, this claim has been cancelled and replaced by a new claim in accordance with the examiner's suggestion.

In view of the above remarks, it is respectfully submitted that Applicants' specification provides sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention. Withdrawal of the rejection under 35 U.S.C. § 112, first paragraph, is respectfully requested.

In addition, to further demonstrate the activity of Applicants' claimed compounds, enclosed herewith is a Declaration by Dr. Simon L. Goodman, one of the co-inventors of the instant application. This Declaration presents test results demonstrating activity of compounds of the claimed invention as being inhibitors of integrin  $\alpha_v\beta_3$ .

Withdrawal of the rejection under 35 U.S.C. § 112, first paragraph, is again respectfully requested.

**Rejection Under 35 U.S.C. § 112, Second Paragraph.**

Claims 1-20 are rejected on grounds of allegedly being indefinite. This rejection is respectfully traversed.

In accordance with the Examiner's suggestion, claims 1 and 20 have been amended to recite singular compounds. It is noted, however, that a compound claim provides protection for the compounds encompassed there regardless of whether the compounds are present in isolated or pure form or whether they are present in the form of a mixture of compounds.

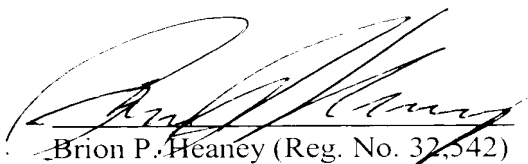
In regards to the derivatives of amino acids recited in claims 1 and 20, Applicants have amended the claims to use language similar to that suggested by the examiner. The definitions of  $R^1$  and  $R^2$  in claims 1 and 20 have been amended to delete the term "also" and to indicate that alternatively these groups can together form one of the indicated structures. With respect to the suggestion that the definition of groups  $R^7$ - $R^{10}$  be preceded by "wherein", it is respectfully submitted that this language is unnecessary. However, if the examiner maintains this suggestion, Applicants will comply. Also, concerning the description of optically active amino acids and amino acid derivatives, claims 1 to 20 are amended above to clarify this description.

Claim 4 is amended to clarify the language thereof. Subsections (a) and (b) are described as alternatives and subsection (c), which describes the formulation of salts, can be used by itself or it can be used in conjunction with the processes described in subsections (a) or (b). Subsection (b) is also amended to further clarify the subject matter thereof. The process of subsection (b) does not necessarily require cyclization step: the starting material is already cyclized, i.e., it is a functional derivative of formula I.

In regards to claim 8, Applicants' specification describes pathologies which are supported or propagated by angiogenesis and further describes how integrin inhibitors can be used to treat such pathologies that are supported or propagated by angiogenesis. In this regard see, for example, Applicants' disclosure at page 2, line 37 - page 4, line 6. Thus, it is respectfully submitted that one of ordinary skill in the art can readily determine the literal scope of the claim.

In view of the above remarks, withdrawal of the rejections under 35 U.S.C. § 112, second paragraph, is respectfully requested.

Respectfully submitted,

A handwritten signature in black ink, appearing to read "Brion P. Heaney", is written over a horizontal line.

Brion P. Heaney (Reg. No. 32,542)  
Millen, White, Zelano & Branigan, P.C.  
Arlington Courthouse Plaza I, Suite 1400  
2200 Clarendon Boulevard  
Arlington, VA 22201  
Tel: (703) 812-5308  
Fax: (703) 243-6410  
E-mail: [heaney@mwzb.com](mailto:heaney@mwzb.com)

**Filed: July 30, 2001**

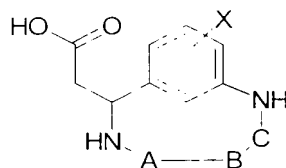
BPH(pdr) K:\Merck 2075\Amend 7-30-01.wpd

**VERSION WITH MARKINGS TO SHOW CHANGES MADE**

**In The Claims**

**Please amend claims 1, 3, 4, 6-10 and 20 as follows:**

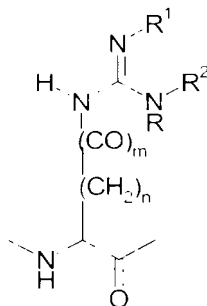
1. A compound ~~Compounds~~ of the formula I



in which

A is Gly, Ala, derivatized Gly, derivatized Ala or NH-NH-CO, ~~where the amino acids mentioned can also be derivatized.~~

B is a radical of the formula II



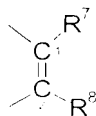
C is  $-(CO)_p-(CH_2)_q-(CO)_r-$  or  $-(CO)_p-CH=CH-(CO)_r-$ ,

m, p, r are in each case independently of one another 0 or 1,

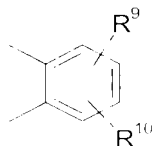
n, q are in each case independently of one another 1, 2, 3, or 4,

R<sup>1</sup> and R<sup>2</sup> are independently of one another H or alkyl, or

R<sup>1</sup> and R<sup>2</sup> can together be ~~are also~~



or



R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup>,

and R<sup>10</sup> ~~in each case are each,~~ independently of one another, ~~are~~ H, alkyl, Ar, OR<sup>6</sup>, Hal, NO<sub>2</sub>, NR<sup>6</sup>R<sup>6</sup>, NHCOR<sup>6</sup>, CN, NHSO<sub>2</sub>R<sup>6</sup>, COOR<sup>6</sup> or COR<sup>6</sup>,  
 X is H, Hal, alkyl or Ar,  
 Ar is phenyl which is unsubstituted or mono-, di- or trisubstituted by R<sup>3</sup>, R<sup>4</sup> or R<sup>5</sup> or is unsubstituted naphthyl,  
 R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup> ~~in each case are each,~~ independently of one another, ~~are~~ R<sup>6</sup>, OR<sup>6</sup>, Hal, NO<sub>2</sub>, NR<sup>6</sup>R<sup>6</sup>, NHCOR<sup>6</sup>, CN, NHSO<sub>2</sub>R<sup>6</sup>, COOR<sup>6</sup> or COR<sup>6</sup>,  
 R<sup>6</sup>, R<sup>6'</sup> ~~in each case are each,~~ independently of one another, ~~are~~ H, alkyl, phenyl or benzyl, and  
 Hal is F, Cl, Br or I,

and if there are radicals of wherein optically active amino acids ~~and amino acid or derivatives, both the~~ thereof can be in either their D and the or L forms; ~~are included;~~ and their physiologically acceptable salts thereof.

2. ~~An enantiomer of a diastereomer of a~~ A compound ~~of the formula~~ according to Claim 1, wherein said compound is in the form of a single enantiomer or single diastereomer.

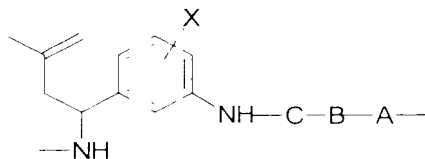
Please cancel claim 3 without prejudice or disclaimer.

4. A process ~~Process~~ for the preparation of ~~compounds of the formula I a~~ compound according to Claim 1 ~~and of their salts, characterized in that~~ comprising (a) treating with a cyclizing agent a compound of the formula III

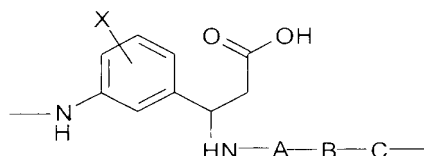
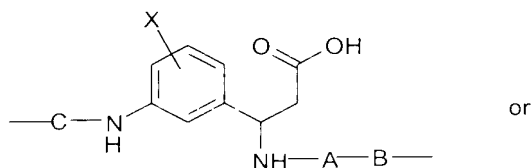
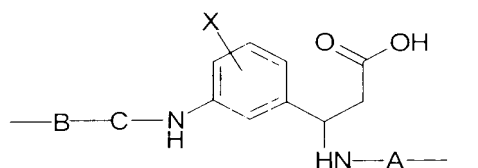


in which

Z is







and X, A, B and C have the meanings indicated in Claim 1, or a reactive derivative of a compound of the formula III, to obtain a compound according to claim 1, or is treated with a cyclizing agent, and or

- b) treating a functional derivative of a compound of the formula I ~~is set free from one of its functional derivatives by treating~~ with a solvolysing or hydrogenolysing agent, to obtain a compound according to claim 1, and/or
- c) ~~in that~~ converting a basic or acidic compound of the formula I ~~is converted~~ into one of its salts by ~~treating~~ treatment with an acid or base.

5. A process ~~Process~~ for the production of a pharmaceutical ~~preparations~~ characterized in that, preparation comprising bringing a compound ~~of the formula I~~ according to Claim 1 ~~and or one of its physiologically acceptable salts is brought~~ into a suitable dose form together with a least one solid, liquid or semi-liquid excipient or auxiliary.

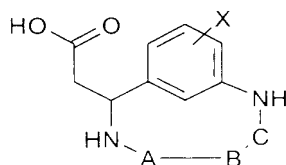
6. A pharmaceutical composition, comprising at least one compound according to Claim 1, and at least one excipient suitable for sustained administration, parenteral administration, topical application, or administration by inhalation spray.

7. ~~Compounds of the formula I according to Claim 1 and their physiologically acceptable salts as integrin inhibitors~~ A method for the control treatment of diseases of the circulation, thromboses, cardiac infarct, coronary heart diseases, arteriosclerosis, apoplexy, angina pectoris, tumours, osteoporosis, inflammations, infections ~~and or~~ resenosis after angioplasty, comprising administering to a patient in need thereof an integrin inhibitory effective amount of a compound according to claim 1.

8. A method for the treatment of ~~Use of compounds of the formula I according to Claim 1 and/or their physiologically acceptable salts in~~ pathological processes which are supported or propagated by angiogenesis, comprising administering to a patient in need thereof of an effective amount of a compound according to claim 1.

Please cancel claims 9 and 10 without prejudice or disclaimer.

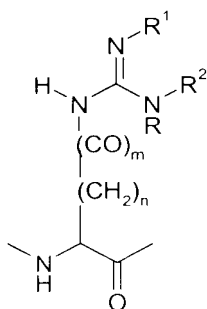
20. A compound ~~Compounds~~ of the formula I



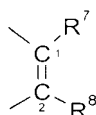
in which

A is Gly, Ala, derivatized Gly, derivatized Ala or NH-NH-CO, ~~where the amino acids mentioned can also be derivatized.~~

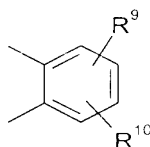
B is a radical of the formula II



C is  $-(CO)_p-(CH_2)_q-(CO)_r-$  or  $-(CO)_p-CH=CH-(CO)_r-$ ,  
 m, p, r are in each case independently of one another 0 or 1,  
 n, q are in each case independently of one another 1, 2, 3, or 4,  
 $R^1$  and  $R^2$  are independently of one another H or alkyl, or  
 $R^1$  and  $R^2$  can together be



or



$R^7$ ,  $R^8$ ,  $R^9$ ,  
 and  $R^{10}$  are each, in each case independently of one another, ~~are~~ H, alkyl, Ar,  $OR^6$ , Hal,  
 $NO_2$ ,  $NR^6R^6$ ,  $NHCOR^6$ , CN,  $NHSO_2R^6$ ,  $COOR^6$  or  $COR^6$ ,  
 X is H, Hal, alkyl or Ar,  
 Ar is phenyl which is unsubstituted or mono-, di- or trisubstituted by  $R^3$ ,  $R^4$  or  $R^5$   
 or is unsubstituted naphthyl,  
 $R^3$ ,  $R^4$ ,  $R^5$  ~~in each case~~ are independently of one another ~~are~~  $R^6$ ,  $OR^6$ , Hal,  $NO_2$ ,  $NR^6R^6$ ,  
 $NHCOR^6$ , CN,  $NHSO_2R^6$ ,  $COOR^6$  or  $COR^6$ ,  
 $R^6$ ,  $R^6$  ~~in each case~~ are independently of one another ~~are~~ H, alkyl, phenyl or benzyl,  
 and  
 Hal is F, Cl, Br or I.

~~and if there are radicals of wherein~~ optically active amino acids and ~~amino acid~~ derivatives thereof can be in either their ~~both the D and the or L forms; are included~~, and their salts thereof.

**Please add the following new claims:**

21. A pharmaceutical composition comprising at least one compound according to claim 1 and at least one solid, liquid or semi-liquid excipient .

22. A process for the preparation of a compound according to claim 1 comprising

(a) cyclizing a compound of formula III in the presence of a cyclizing agent for a time and under conditions effective to obtain a compound according to claim 1; and

(b) isolating the compound of claim 1.

23. A compound according to Claim 1:

a) (8S,14S)-2-(8-(3-guanidinopropyl)-3,6,9,12-tetraoxo-2,7,10,13-

tetraazabicyclo[13.3.1]nonadeca-16,18,19-trien-14-yl)acetic acid or a physiologically acceptable salt thereof;

b) (9S,15S)-2-(9-(3-guanidinopropyl)-3,7,10,13-tetraoxo-2,8,11,14-

tetraazabicyclo[14.3.1]eicosan-17,19,20-trien-15-yl)acetic acid or a physiologically acceptable salt thereof;

c) (8S,14S)-(8-(3-guanidinopropyl)-18-methyl-3,6,9,12-tetraoxo-2,7,10,13-

tetraazabicyclo[13.3.1]-nonadeca-1(18),15(19),16-trien-14-yl)acetic acid or a physiologically acceptable salt thereof;

d) (6S,12S)-(6-(3-guanidinopropyl)-4,7,10-trioxo-2,5,8,11-

tetraazabicyclo[11.3.1]heptadeca-1(17),13,15-trien-12-yl)acetic acid or a physiologically acceptable salt thereof..